DR. MACIAS: Yes, I think it is very difficult to interpret the DNR rates between the two groups because the DNR rate may reflect the fact that you gave them placebo and not effective therapy. The incident rate of making someone -- DNR may go down in the setting of an effective therapy.

DR. RELLER: Dr. Leggett?

DR. LEGGETT: A couple of questions. In terms of the survival benefit, it appeared that most of the time in the Kaplan-Myer curve that the survival benefit happened after the infusion. So, I would take that sort of physiologically to mean as you, I think tried to show that it was less organ dysfunction down the road, and you made the statement in, I cannot remember the slide where the post-5-day-infection rates, post-baseline infection rates were the same. Was the post-baseline mortality from those infections the same as part of that first question?

The second part of that first question is when people went back and looked at these patients in terms of other routine care, were the assessments of optimal or appropriate antibiotics in the two groups controlled for or looked at to see if that could be a potential confounding variable much like the steroid question?

DR. MACIAS: The answer to the very first question which is what were the mortality rates between treatment groups for patients having a post-baseline new infection,

did we look at that, Jeff, do you remember? I don't think we looked at that. We can look at that for you today.

To answer your second question, and that is the appropriateness of antibiotics, all of the case report forms were reviewed by our Clinical Evaluation Committee and appropriateness of antibiotic therapy was adjudicated by the CEC.

Approximately 88 percent of patients received appropriate antibiotic therapy within 24 hours of the diagnosis of severe sepsis, and the proportion was equal between the two treatment groups, and by 48 hours 92 to 93 percent of patients had received appropriate antibiotic therapy.

You can bring the slide up?

This slide just shows you the relative risk associated with drotrecogin alfa (activated) for patients who had received appropriate therapy within the 48-hour period.

DR. LEGGETT: I knew that. I was talking specifically about the post-baseline infections, in other words, afterwards.

DR. MACIAS: Dr. Levy, could you remind me? The adequacy of antibiotics was adjudicated for the original infection. I don't believe it was adjudicated for subsequent infections.

DR. LEVY: That is correct.

DR. LEGGETT: The next simple question, was the same D-dimer test, I understand there are several or at least a couple of them, was the single test done for everything or was it site specific and variable?

DR. MACIAS: Those were central laboratory data. So, it was the same for all patients.

DR. LEGGETT: I noticed in terms of infection there was a relatively low number of blood culture sites of infection. Does that mean those were primary intravascular infections and not sort of bacteremia related with pneumonia, for instance?

DR. MACIAS: No, what you are looking at there I think is just blood culture positive.

DR. LEGGETT: So, only 10 percent of this group was blood culture positive basically?

DR. MACIAS: Jeff, could you --

DR. LEGGETT: Because that seems to be a pretty low number for severe sepsis.

DR. MACIAS: Could I see the treatment analysis by blood culture positive, blood culture negative?

DR. HELTERBRAND: Positive blood culture is about 30 percent of the population, but we can show the slide with the data.

DR. MACIAS: You can bring that up for me, please?

DR. LEGGETT: So, this Page 18, Slide 36 is primary, okay.

DR. MACIAS: I am sorry. I think I misunderstood what you were asking me, but you can look at this slide and you can see that between the two treatment groups approximately, well, 266 patients of the drotrecogin alfa (activated) and 275 of the placebo group had positive blood cultures. That is the relative risk. The remaining patients of course, had negative blood cultures. That is the relative risk, and then since we are here you can look at whether they had any culture positive or had no culture positive and this is the relative risk.

DR. LEGGETT: Final question, in comparing the pediatric group in terms of demographics to the adult group I noticed that the types of infections were different. In the adult group your UTI mortality was much lower as we would expect from other mortalities. In the pediatric group which had relatively more kinds of infections, Slide 91, do we know about relative mortality in pediatric groups or in other adult sepsis groups, relative to the mortalities of central nervous system and the blood site of infection as opposed to lung?

DR. MACIAS: For pediatric patients in general?

DR. LEGGETT: Either pediatric or other adult things looking at those questions since to me these

demographics do not match up.

DR. MACIAS: Brett, would you like to address an estimated mortality rate for pediatric patients with central nervous system infection?

DR. GIROIR: The estimated mortality rates in this trial according to the Pediatric Index of Mortality for CNS infections was approximately 18 percent. The overall mortality in pediatric patients in this trial really matches previous experience in pediatrics that the overall mortality rate despite similar numbers of organ failure and similar severity of illness is less in the pediatric population than it is in adults, and one might conjecture the reasons for that.

DR. MACIAS: That is Dr. Giroir. I am sorry, I should have probably introduced you rather than saying just, "Brett, could you go to the microphone," and Dr. Giroir has been the principal investigator for the Pediatric Development Program at Lilly.

DR. RELLER: We will have two final questions, then a 10-minute break and the FDA presentation. Dr. O'Fallon?

DR. O'FALLON: Dr. Fleming has assured me that you used the O'Brien-Fleming rules properly which is excellent to hear

DR. MACIAS: I have to ask Dr. Helterbrand that

question.

DR. O'FALLON: The coincidence of the change in the protocol at approximately the same time that the first interim analysis was performed has bothered me as I read this material, and the fundamental question is, and I assume that the Committee when they did the second interim analysis did understand that there had been major changes in the protocol and attempted to take that into account as they made their recommendations. Is that correct?

DR. MACIAS: Dr. Opal, would you like to address that question, please?

Dr. Opal was the Chairman of the DMSB.

DR. OPAL: Yes, we were aware of the protocol amendment and did take that into consideration in looking at the data.

DR. RELLER: Dr. Ebert?

DR. EBERT: This is a follow-up question to a comment by Dr. Helterbrand. I wanted to get a little more information about the multivariate analysis that you referred to. Were you able to in a multivariate manner determine what risk factors or measures of severity of the illness were important in determining mortality or were related to the mortality and where did drug treatment fall as far as the relative measure on impact on mortality?

DR. HELTERBRAND: Yes, please, slide on?

Just to give brief details, we used a common approach to model selection using stepwise multiple logistic regression. Intuitively covariates are included in this model based on their explanatory value as you alluded to earlier.

Next slide, please?

We actually considered 21 different variables for inclusion in the model, including some patient demographics, some baseline data in terms of patient location, morbidity status, functional dependency status, infection site and type and surgical status, several clinical markers of disease severity and several biochemical markers of disease severity to be considered.

Next slide?

We, also, considered all two-factor interactions to be included in the model such as an age-by-treatment interaction if it had been present or an age by gender. So, they were all included in the stepwise procedure. We used the Schwartz(?) criterion to select our method or to select our final model, and we used forward and backward steps as is customly done in stepwise regression.

We, also, used the goodness of fit statistic, the most commonly used one which is the Honemere-Lamenshaw(?) chi square statistic.

Next slide, please?

Here is your point which is what were the results. The following covariates were retained in the model, age, APACHE II score, prothrombin time and we did the IL-6 on a log scale due to its distribution, dependency status and whether you have urosepsis or not.

The goodness of fit statistic to support the model's adequacy was .50. So, it supports the model's accuracy I suppose and basically this model estimated a constant 40.2 percent increase in the odds of survival with Xigris across the population. Importantly no interaction terms were included and no treatment by covariate interactions were included in the resulting model.

DR. RELLER: This concludes the Lilly presentation and the discussion related thereto.

We will have a 10-minute break. Please return promptly after that for the start of the FDA presentation.

(Brief recess.)

Agenda Item: FDA Presentations

DR. RELLER: We will begin with Dr. Linda Forsyth who is an officer with the Center for Biologics Evaluation and Research, FDA.

Dr. Forsyth?

DR. FORSYTH: Thank you very much.

Good morning. My name is Dr. Linda Forsyth. I am a medical officer in the Center for Biologics. This

presentation is divided into two parts. I will begin by presenting the efficacy. Dr. Robert Lindblad will follow me and present an overview of the pediatric program and follow with the adult safety data.

As you have already heard the sponsor is proposing drotrecogin alfa or rhAPC recombinant human activated protein C be indicated for the treatment of pediatric and adult patients with sepsis associated with acute organ dysfunction or severe sepsis and that treatment with rhAPC reduces mortality in patients with severe sepsis.

The sponsor has conducted a number of trials. As you can see this includes a number of small Phase I uncontrolled trials. These included clinical, pharmacology studies, studies with end-stage renal disease, patients with protein C deficiency and purpura fulminans.

The sponsor, also, conducted a single-controlled Phase II trial of 131 patients with severe sepsis. A single randomized controlled trial, Phase III trial was performed in 1690 patients. A pediatric study was performed in 83 children with severe sepsis and finally there occurred ongoing uncontrolled trials having enrolled over 500 patients thus far.

The focus of my presentation will be on the Phase III data, but I will begin this section with a few Phase II slides.

So, again, the Phase II study was a randomized placebo-controlled dose-ranging multicenter trial. The study was conducted in 131 patients with severe sepsis; rhAPC was given in four different doses. This was given as a continuous intravenous infusion for either 48 or 96 hours. The outcomes measured in this trial were pharmacodynamic and pharmacokinetic as well as safety.

This table shows mortality from the Phase II study. As you can see 29 percent of the patients receiving any dose of rhAPC died compared to 34 percent of the patients receiving placebo.

This result was not statistically significant. Dr. Lindblad will describe the safety data in his presentation. The sponsor has already shown the pharmacodynamic and pharmacokinetic data from the study which I will not go into here. The dose for the Phase III trial was chosen due to the pharmacodynamic effects based on D-dimers in the Phase II trial, and just to recap what you have already heard from the sponsor, the Phase III study designated as EVAD was a randomized double-blind, single-dose, placebo-controlled, multicenter trial. The dose administered was 24 micrograms per kilo as a continuous 96-hour intravenous infusion in patients with severe sepsis.

Two thousand two hundred and eighty patients were originally planned for enrollment into the study. The

diagnosis for severe sepsis was defined as patients meeting three or four systemic inflammatory response syndrome criteria, plus at least one organ failure and suspected or proven infection.

Patients that were at a high risk of bleeding were excluded from the study. Again, the primary efficacy end point for the study was 28-day all-cause mortality. The primary efficacy analysis included Cochran-Mantel-Haenszel test stratified by pre-infusion APACHE II quartile, age class, that is than 60 years of age and over 60 years of age and protein C activity class.

There were two planned interim analyses prospectively defined, identified by the sponsor. The first interim analysis occurred after 760 patients were treated. The second interim analysis occurred after 1520 patients were treated in June 2000.

The O'Brien-Fleming boundary for the alfa thinning function was specified as .0002 and .0118 respectively. The sponsor identified a number of secondary analyses of mortality treatment shown here, including protein C activity and notably APACHE II along with others.

In the next several slides I will present the patient demographics between the two treatment groups, rhAPC and placebo.

This slide shows that age, gender and ethnic

origin were well balanced. There were a large number of pre-existing patient conditions in both treatment groups. Of note most were similar. However, there were some minor imbalances.

This slide highlights a number of the minor differences such as with hypertension, with myocardial infarction and congestive cardiomyopathy as well as others such as chronic obstructive pulmonary disease and cancer.

This slide displays the recent surgical history of patients between the treatment groups. Patients were grouped as to whether they had no history of surgery, required emergency surgery before study drug was administered or whether elective surgery was performed.

These groups were well balanced, and this slide presents measures of disease severity. Of note, both treatment groups had a mean APACHE score of 25. Also, there were slight differences in the number of patients who required mechanical ventilation in shock and with the use of vasopressors.

And lastly, this slide shows the distribution of the number of organ failures between the treatment groups. Both treatment groups are relatively well balanced.

In this table we have presented the results of the primary advocacy end points for the Phase III trial, again, to remind you the primary efficacy end point, 28-day, all-

cause mortality as seen in the last column was reduced in patients that received rhAPC. Twenty-four point seven percent of the patients with severe sepsis died compared to 30.8 percent of the patients that were on placebo. The total number of patients was 1690, and the P value was significant at .005.

This study was stopped at the second interim analysis. These same data are depicted graphically in this Kaplan-Myer curve. As shown already by the sponsor we have in our curve we have the red line represented by rhAPC, the green line by placebo.

Time is presented in days on the X axis and percent survival on the Y axis. As can be seen a clear separation occurs approximately at the end of the first week.

The percent survival scale from the sponsor slightly differed from what we have we have presented here.

As mentioned earlier the sponsor has identified a number of important secondary end points evaluating mortality by patient subgroups. I am now going to review data from a number of these secondary analyses. We will look at age, disease severity, hematologic parameters and also look at the use of heparin.

We will first set off with patient age as highlighted on this slide. The sponsor prospectively defined

in their analytic plan to test for treatment effect by patient age using a cutoff point of 60 years of age as shown in this slide. In the first column this can be seen.

There is a treatment effect in rhAPC in both less than 60 and over than or equal to 60 years of age. However, as seen in the column with the mortality difference the treatment was slightly greater in the older age group with 5 and 7 percent mortality difference respectively.

These same data are shown graphically in this slide. Age in years is plotted on the X axis. Percent mortality is presented on the Y axis and/or the number of patients are shown in brackets below.

There appears to be a greater treatment effect in patients over 50 years of age compared to younger patients. At both ends of the curve, however, you will note there are a small number of patients.

I will now present data on disease severity starting with the APACHE II scores, then will address organ failure and finally shock.

APACHE II or acute physiology and chronic health evaluation is a scoring system developed as a predictor of mortality described by Dr. Knause(?).

In the ICU setting it is comprised of three components, acute physiologic measurements, age and chronic health status. The higher the APACHE score the more severe

the disease.

We evaluated the relationship between treatment benefit and disease severity defined by APACHE II as displayed in this slide. In the first column in this table we have the APACHE II scores divided into quartiles. The first quartile consists of APACHE scores between 3 and 19, the second between 20 and 24, the third between 25 and 29 and the fourth between 30 and 53.

As you know, APACHE II is designed to predict the likelihood of mortality. We have the mortality in each of APACHE quartile for the placebo patients and as would be expected there is an increase in mortality as the APACHE scores increase, 12 percent and we can see it moves down to 26 percent, 36 percent and finally 49 percent. Thus, the APACHE II score did, indeed, predict mortality in this population.

In this column in the rhAPC mortality column we have presented the mortality on rhAPC and once again we can see there is an increase in mortality as we go down. The difference in percent mortality between rhAPC and placebo arms is shown in the third column from the right in percentage. There is a 3 percent higher mortality in the APC arm, in the first APACHE quartile seen here and then a 4 percent lower mortality in rhAPC in the second APACHE II quartile. In the third APACHE quartile we can see a 12

percent reduction and finally an 11 percent reduction, lower mortality in the fourth quartile.

So, as we can see the largest rhAPC effects are in the third and fourth quartiles. The second column from the right is relative risks. We have the corresponding relative risks of death and next to that the 95 percent confidence intervals. Here, too, the data suggest that the greatest rhAPC benefit is in the higher quartiles.

These data suggest an interaction between treatment and APACHE II quartiles of .009. Again, these same data are depicted graphically but this time on the X axis the APACHE scores are divided into finer intervals of 5 units.

Again, rhAPC is in red and placebo in green. The N's in each APACHE interval appear in parentheses below. So, again, those patients with more severe disease appear to have somewhat more of a treatment benefit than those patients with less severe disease.

There are a few patients on either side, you can see here, of the curve of the APACHE scores. So, little can be made of these data.

In this slide we combined the first and second APACHE quartiles and the third and the fourth APACHE quartiles together. As can be seen in the first row here the first and second APACHE quartiles were combined representing

an APACHE score of under 25. In the second row this combined the second and fourth APACHE quartiles together and this represented an APACHE score of 25 or above.

The mortality difference in percentage here presented in the third column from the right we can see there is virtually no difference in the mortality between rhAPC and placebo in the combined first and second quartiles; however, among patients in the third and fourth quartiles the combined APACHE difference or mortality difference, excuse me, was 13 percent.

Another way to capture disease severity and treatment benefit was to investigate the number of organ failures that occurred at baseline.

The first column shows the number of organ failures. Next, looking at the placebo column right here, there is an increase in the mortality rates with the greater number of organ failures as can be seen in this manner.

A similar trend actually occurs with the rhAPC mortality rates. The mortality difference in the third column from the right between rhAPC and placebo show an increase in mortality differences with an increased number of organ failures.

Patients with fewer organ failures at baseline have a suggestion of less of a benefit than with higher. These same data are depicted graphically again here. The

likelihood of benefit appeared to be greater when patients presented with a greater number of organ failures and on to the next slide.

In this slide we have a table that displays mortality as a function of shock. Approximately 70 percent of the patients were in shock as defined by the sponsor within a 6-hour period preceding study drug administration.

In this table we can see mortality as a function of shock. Patients in shock showed a greater difference in mortality on rhAPC versus placebo. Those patients not in shock appeared to show a somewhat small difference.

Next in summary of the treatment effect by APACHE II and organ failure and shock we looked at the predicted values of relative risks and their 95 percent confidence intervals for APACHE and the number of organ failures and shock at baseline.

The data in this slide show the relative risk of death represented by the yellow points and their 95 percent confidence intervals in red.

A logarithmic scale is on the X axis and on the Y axis you need to take the various subgroups. One represents no treatment benefit. Anything to the right the placebo is better and anything to the left the treatment with rhAPC is better, except in the first quartile with a relative risk above one in the first APACHE quartile. The other APACHE

quartiles show treatment benefit less than one. Patients with one organ failure or without shock had a relative risk of close to one. All others showed more treatment benefit with relative risk less than one.

So, in summary patients with more severe disease may suggest a greater treatment effect.

Now, we will proceed to look at hematologic parameters as highlighted here. This slide shows treatment effect as a function of protein C levels at baseline. One might postulate that the relative benefits of recombinant APC therapy be related to the deficiency of this protein in the serum.

In this table there are two main points. Relatively few patients were not protein C deficient at baseline. Also, there appears to be no relationship between protein C deficiency and treatment with rhAPC.

The unknown category was in a small number of patients who did not have tests performed due to laboratory error. So, it was unknown whether the patient was protein deficient or not.

We evaluated treatment benefit by disseminated intravascular coagulation or DIC. The majority of patients in this trial, over 90 percent had laboratory evidence of DIC at study entry. This was defined by the presence of at least two of four laboratory findings as the sponsor has

previously defined today.

There were 115 patients in which DIC was unknown or absent. In 113 patients of this group this was due to insufficient laboratory data available to determine DIC. Of the small number of patients there appears to be a limited treatment effect in this group.

Finally, the use of heparin. Use of therapeutic heparin was an exclusion criteria. Low-dose heparin was permitted in the trial and about two-thirds of the patients received heparin. In this analysis we explored whether the use of heparin impacted the size of mortality benefits attributable to rhAPC. RhAPC mortality results in patients on low-dose heparin were compared to those in patients not on low-dose heparin.

Low-dose heparin use was categorized in two different manners, use at baseline as shown at the top and during infusion underneath.

While the second group, that is the group that includes patients who had heparin begun during the study drug administration is the group of greatest interest inclusion of such patients may introduce biases if the use of study drug influenced the decision to start heparin. Therefore both analyses are shown.

As can be seen the mortality effect of rhAPC was 3 to 4 percent in patients on low-dose heparin by either

approach, whether it is baseline or during infusion.

In contrast the mortality of effect of rhAPC was considerably higher in patients that were not on low-dose heparin. You can see the difference is 9 to 15.

So, to summarize mortality in patients who received rhAPC was lower than placebo regardless of whether low-dose heparin was used or not, but treatment benefit was several-fold greater in patients that were not on low-dose heparin. However, the study to note was not designed to assess whether low-dose heparin should be used with rhAPC.

I would now like to switch gears and focus not only on mortality but on morbidity. Since 20-day all-cause mortality does not reflect all outcomes of treatment benefit it is important not only to look at the number of patients alive but at their treatment status and evidence of comorbidity.

Shown here in this slide is a side-by-side comparison of morbidity and functional status at day 28 compared between rhAPC and placebo. Mortality is shown in red. In green we have a side-by-side comparison of ICU status at day 28.

In yellow patients that are still hospitalized at the end of the study are shown. Violet is patients that are in a nursing home and navy in a discharged home.

In the rhAPC arm there was as you can see

approximately a 6 percent difference of fewer patients who died on study. At day 28 this group had about a 2-1/2 percent number of more patients that were alive in the ICU and alive in hospital.

Also, about a 1 percent difference occurred in patients that were discharged to a nursing home or to home.

Finally, before I conclude with the summary of efficacy I would like to focus on the changes that were made to the protocol by the sponsor. These occurred while the study was still blinded and before the first interim analysis was conducted. The sponsor made two sets of changes in July 1999.

They altered their analytic time and they clarified their inclusion and exclusion criteria and they eliminated protein C deficiency and septic shock from the Cochran-Mantel-Haenszel test.

The sponsor changed the inclusion and exclusion criteria to clarify certain parameters. This was done to clarify definitions and better eliminate patients with chronic or comorbid disease. These patients were not likely to respond from acute therapy of severe sepsis in the sponsor's evaluation.

Listed here are some of the criteria that were modified. These include excluding patients that were more likely to bleed such as patients with esophageal varices or

cirrhosis. They also excluded patients that were more likely to die and patients with other underlying disease such as malignancies and, also, they further clarified their organ failure eligibility for the trial.

These are the results of the changes between the original and amended protocol. There were a few relative modest differences between the original as compared to the amended version of the protocol.

In the amendment there were fewer patients with malignancies that were immunosuppresed that had the withdrawal of life support, with chronic APACHE health points and with non-sepsis-related disease as well as at nursing home facilities.

Also, of note a few points, the IL-6 median level was slightly higher in the amended protocol compared to the original. The mean APACHE scores between the original and the amended version were the same at 25. Acidosis was more common under the original protocol compared to the amended.

We, also, looked at the differences between the number of "do not resuscitate" orders under the original versus the amended version of the protocol.

As can be seen the placebo rates were similar. However, the number of patients in the first half of the study or in the original protocol on rhAPC it was 16 percent compared to 10 percent in the second half of the study or

under the amendment.

This may reflect differences in mortality as on the next slide. Here as previous touched upon this table displays mortality data stratified by the original and the amended versions of the protocol. As we can see there were 720 patients that were enrolled in the original protocol and 920 under the amendment.

The placebo rates between the two protocol versions are similar. However, in the rhAPC arm there was a 28 percent difference in mortality under the original protocol compared to 22 percent in the amended version of the protocol. As noted we, also, have the P values here of .0055 or .057. Under the original protocol and under the amended protocol we have a P value of .00012.

It is, however, important to review not just the individual landmark analyses of the data for specific patients but to look over the entirety of the survival curves as a function of study day.

Shown in this table as the sponsor has already shown are the mortality rates in each arm on day 1 and really on a day-to-day basis as the study was conducted.

On the X axis we have the dates throughout the study. On the Y we have the mortality rates depicted for each study arm reflecting 28-day observation and therapy.

Let me go ahead and point out a few salient

features. Line A represents the time the first patient was enrolled under the amended version of the protocol.

Line B occurs when the first interim analysis occurred and Line C when the second interim analysis occurred.

Of note, there was a separation of the curves before the protocol amendment was implemented in favor of benefit for rhAPC. These curves continued to separate throughout as the study progressed.

This curve was conducted in 1690 patients and slightly differs from the sponsor's curve presented earlier today as the numbers differ. The sponsor apparently was using a number of sites, of 99 sites and 1493 patients, and furthermore we conducted a sensitivity analysis evaluation for those patients that were enrolled in the original protocol, but would have been excluded from the amended protocol.

There were a total of 81 patients or 11 percent that did not meet new inclusion criteria for the amended protocol that would have met the original protocol.

Despite the 81 patients who did not meet the inclusion criteria they continued to show treatment effect. So, in summary there was a benefit in the 28-day all-cause mortality. The mortality rate on rhAPC was 24.7 percent versus the 30.8 percent on placebo with a P value of .005.

Finally treatment benefit was more predominant in the following groups of patients, in the third and fourth APACHE quartiles compared to the first and second, in patients with laboratory evidence of DIC compared to those without and also in patients receiving heparin, oh, not on heparin, excuse me, compared to those receiving low-dose heparin, in age groups over 50 years of age compared to not and in greater than two organ failures at baseline compared to patients without or single organ failure and finally, in patients with shock compared to patients without shock.

Next, Dr. Lindblad will present pediatric and safety data.

DR. LINDBLAD: I was going to start off with good morning, but I think I will start with good afternoon.

I would like to present data on both the pediatric patient population studied by the sponsor and the adult safety in the Phase II and Phase III trials.

This will be followed by immunogenicity data and a summary of the presentation. It is important to note that there are no randomized placebo-controlled trials in the pediatric patient population. The uncontrolled pediatric study was ongoing at the time of the BLA submission and the final report has not yet been filed with the agency.

The sponsor is seeking a pediatric indication based on demonstrating the similarity of pediatric sepsis to

adult sepsis. This is based on the sponsor's premise that the disease characteristics, the pharmacokinetics and pharmacodynamic data as previously described by the sponsor are the same, as well an adequate safety database at the recommended dose and duration of treatment.

Since APACHE II scores are not used in pediatric patients the pediatric index of mortality was used. In addition to the pediatric index of mortality disease severity can be estimated by the number of organ failures and the overall mortality that was observed.

The total pediatric safety database consists of 121 patients. The sponsor presented a slightly higher number based on the ongoing trials. The pediatric patient population was studied primarily in an 83 patient safety and pharmacokinetic pharmacodynamic sepsis trial as previously described by the sponsor.

An additional 14 pediatric patients were enrolled in the study of patients with purpura fulminans and finally there are ongoing safety open-labeled trials that have enrolled at my time 24 additional pediatric patients.

These next slides compare the 83 pediatric patients enrolled in the primary pediatric sepsis trial to the adult patients enrolled in the Phase III trial.

The first two slides have a pediatric database of 32 patients. These patients were enrolled after a protocol

amendment that added both hematologic and renal organ failure and more closely mirrored the adult study. The last three slides are based on the entire 83 pediatric patients enrolled in the study.

This first slide based on the 32 patients enrolled after the amendment compares the type of organ failure seen in the pediatric patients compared to the adult patients.

Pediatric patients had cardiovascular organ failure more often and respiratory organ failure less often when compared to the adults.

In addition renal failure was less common in the pediatric patients compared to the adult patients.

The next slide, also, based on the 32 patients enrolled after the amendment shows the number of organ failures in pediatric sepsis compared to adult sepsis.

This is one marker of disease severity, and it shows a shift to a single organ failure for the pediatric patients as compared to multiple organ failure in the adult patients in the Phase III trial.

The next slide, based on the 83 patient pediatric database compares the primary sites of infection in the pediatric population versus the adult population. The primary site of infection was blood followed by pneumonia and meningitis for the pediatric patients.

Blood and CNS primary sites of infection are

uncommon in adult patients. As would be expected adult patients had primarily pneumonia, intra-abdominal and urinary tract infections.

Again, based on the 83 patient pediatric database the type of pathogen is more often gram negative as compared to gram positive in the adult patients.

The pediatric index of mortality was used in the pediatric sepsis study. This index was developed to predict mortality in the intensive care unit. The pediatric index of mortality score in the pediatric patients was 11 percent overall.

The APACHE II score was used in adults and estimated a mortality of 25 percent. Though these scoring systems cannot be compared directly they suggest a less ill pediatric population.

The mortality data in the pediatric study was determined at day 14. For comparative purposes the 14-day mortality figure was, also, used from the adult trial.

The 14-day mortality for the pediatric patients was 10 percent compared to 20 percent in the adult patients. This, again, suggests a pediatric patient population that is less ill than the adult patient population.

Moving next into the safety data for the pediatric patients a comparison of safety parameters between the pediatric and adult patients reveals similar overall rates

of serious bleeding events, bleeding adverse events, serious adverse events and adverse events between the pediatric and adult patients.

Specific pediatric safety events included one intracranial hemorrhage. The patient, a 14-year-old with meningococcemia died on study day 13 with a CT scan revealing a right frontal parenchymal hematoma of uncertain age but perhaps a week old. The rhAPC had been stopped 10 hours into the infusion due to anisocoria.

Additionally there were three serious bleeding events noted in the study for a rate of 3.6 percent.

In summary there was a small uncontrolled pediatric database on which to draw any conclusions. Drug effects as reflected by the PKPD data presented by the sponsor and bleeding events were similar between the pediatric and adult patients studied.

There was one intracranial hemorrhage. However, the sepsis disease parameters in the pediatric patients are different than those in the adult patients studied.

The pediatric sepsis patients more commonly had cardiovascular organ failure versus both cardiovascular and respiratory organ failures as was seen in the adults. Pediatric patients had a single organ failure more often than multiple organ failures.

The primary sites of infection were blood followed

by lung and CNS for the pediatric population versus lung, intra-abdominal and urinary tract infections for adults, and finally the 14-day mortality in the pediatric patient population was 10 percent versus a 14-day mortality of 20 percent in the adult patients treated with rhAPC.

Next, I will present the adult safety data starting with the Phase II trial. The patient population chosen for this trial as well as for the Phase III trial excluded patients that were at high risk for bleeding events. These exclusions included major surgery within 12 hours or an anticipated major surgery, GI bleeding within 6 weeks of study entry, trauma patients at increased risk for bleeding and patients with congenital bleeding diathesis. Additionally, patients treated with greater than 650 milligrams of aspirin within 3 days of entry, therapeutic heparin or warfarin within 7 days were excluded.

In the Phase II study specific criteria were used to start and stop the infusion based on the type of procedure and coagulation status.

The infusion was stopped for invasive procedures and restarted immediately after minimally invasive procedures and up to 12 hours after major surgery. The coagulation parameters used to start and stop the infusion included two or more consecutive activated partial thromboplastin times greater than 100 seconds or an INR

greater than 3 or a platelet count less than 15,000.

For the Phase II trial the 28-day mortality was divided into groups based on several factors including the duration of the infusion. RhAPC was administered initially in a dose escalation scheme as described by the sponsor.

All dose groups were sequentially enrolled and received a 48-hour infusion. After safety review new groups were sequentially enrolled and received a 96-hour infusion. The 30-microgram-per-kilogram-per-hour dose was not studied in the 96-hour infusion.

Though the numbers are small there was a suggestion of a higher 28-day mortality in the patients receiving a 96-hour infusion compared to the 48-hour infusion. The overall mortality in the placebo group was 34 percent.

As noted on this next slide there was a higher incidence of serious adverse events in patients that received a study drug for 96 hours than those that received the infusion for 48 hours. The placebo rate was 24 percent.

Three significant bleeding events occurred, two in the 48-hour infusion group and one in the 96-hour infusion group. There were no intracranial hemorrhages.

Next, I will turn to the adult safety data in the Phase III trial. In the Phase III trial there were four deaths attributable to bleeding which occurred during the

infusion period. The infusion period was defined as the start of the study drug through completion plus the next calendar day.

All four deaths occurred in the rhAPC-treated patients. Two of these deaths were due to intracranial hemorrhages representing a rate of 0.2 percent. There was one fatal pulmonary hemorrhage and one death related to an intrathoracic bleed in a patient that had been involved in a significant motor vehicle accident 3 days prior to being enrolled in the study.

On August 28, of this year, the company submitted additional preliminary data regarding intracranial hemorrhages in ongoing post-Phase III safety studies. These studies which are separate from the Phase III trial have similar entry criteria to minimize the risk of bleeding.

Despite these measures 13 new intracranial hemorrhages have been reported with 8 of those occurring during the infusion time period. The remainder occurred between days 7 through 13.

For those bleeds occurring during the infusion the event rate is 1.5 percent. This compares to a rate of 0.2 percent in the Phase III trial.

No other safety data has been submitted related to this patient population in these ongoing studies. The sponsor has, also, been evaluating this data on an ongoing

basis. So, there may be updated information from the sponsor related to these events that has not been formally reviewed by the agency.

Serious bleeding events were defined in the Phase III trial as any intracranial bleed, any life-threatening bleed, transfusion of greater than or equal to 2 units of packed red blood cells in the Phase II trial or greater than or equal to three units of packed red blood cells on two consecutive days for the Phase III trial or they would meet other criteria for a serious adverse event such as a life-threatening event, prolongation of hospitalization, persistent or significant disability, congenital anomaly or birth defect, an event that results in cancer or an event that suggests a significant hazard, contraindication or side effect.

The number of total serious bleeding events during the infusion period was 20 in the rhAPC treated group compared to 8 in the placebo arm. Their GI bleeds were fairly balanced. There was a greater number of intrathoracic bleeds, retroperitoneal bleeds, intracranial hemorrhages and genitourinary bleeds in the rhAPC-treated patients versus the placebo patients.

Adverse events occurring during the infusion period revealed almost twice the rate of serious bleeding events and bleeding adverse events in the rhAPC-treated

patients compared to placebo patients.

The rhAPC and placebo groups were similar with respect to the number of serious adverse events and adverse events.

As was shown in Dr. Forsyth's presentation mortality on treatment was not lower than placebo in the first APACHE II quartile.

This slide shows both the bleeding adverse events and serious bleeding events in the first APACHE II quartile. In a population where rhAPC was not associated with a lower mortality it was associated with more frequent bleeding events. There were 38 bleeding adverse events in the rhAPC arm versus 17 in the placebo arm and 9 serious bleeding events for the rhAPC-treated subjects versus none in the placebo group.

This resulted in a treatment difference of 9 percent for bleeding adverse events and 4 percent for serious bleeding events.

During the 28-day study period multiple transfusions of packed red blood cells fresh frozen plasma and platelets were given. These numbers, again, highlight the greater bleeding incidence in the rhAPC-treated patients as manifested by the greater number of required transfusions.

One must keep in mind that a greater proportion of

the rhAPC-treated patients survived to day 28. This would potentially increase the total number of transfusions given in the rhAPC-treated arm.

Subjects with laboratory evidence of DIC as defined by the sponsor represented over 90 percent of the patients studied. It is unknown how many people were not in DIC as the remaining patients had insufficient data to establish the diagnosis.

The overall rate of serious bleeding events was similar between those that were in DIC and those where the DIC status was unknown.

This rate was twice as high in the rhAPC-treated patients versus the placebo patients. Adverse bleeding events in relationship to baseline coagulation factors are presented next. This data is pooled from the Phase II and Phase III trials. This yields a total of 940 patients in the rhAPC arm versus 881 in the placebo arms.

The actual numbers in each group vary slightly because of patients that had incomplete laboratory evaluations.

For those subjects treated with the rhAPC and a baseline APTT less than 2 times the upper limit of normal the adverse bleeding event rate was 18 percent compared to a 20 percent rate in patients with an APTT greater than 2 times the upper limit of normal.

Both of these are greater than the corresponding placebo rates of 11 and 14 percent respectively.

For subjects with a PT greater than 1.2 times the upper limit of normal there was an increased risk of bleeding in the rhAPC group compared to placebo and compared to subjects that received rhAPC with a PT of less than 1.2 times the upper limit of normal.

A few subjects had platelet counts less than 50,000. In subjects with a platelet count greater than 50,000 there was an increased risk of bleeding in the rhAPC subjects when compared to placebo. There was, also, an increased bleeding risk in the few patients with platelet counts below 50,000 in both the placebo arm and the rhAPC arm.

The next two slides present the serious bleeding events on slide 1 and the bleeding adverse events on slide 2 in those patients treated with heparin while receiving rhAPC or placebo.

Therapeutic heparin was an exclusion criterion for the study. Low-dose heparin was permitted. With a potential for synergistic activity between heparin and rhAPC safety data were reviewed.

The rate of serious bleeding events was increased in the rhAPC-treated patients compared to placebo regardless of receiving heparin.

There was, also, an increased rate of bleeding adverse events for all patients receiving rhAPC whether or not they received heparin.

Reviewing data in subgroups based on gender, origin and age no differences in safety profile were observed.

Using pooled data from the Phase II and III trials patients were grouped based on their surgical status, either having had emergency surgery or elective surgery. These patient characteristics were obtained from the APACHE II assessment and were not prospectively defined.

Other than recording the APACHE II score at the entry of the trial the timing of the surgical procedure is unknown.

Though the numbers are small and the confidence intervals are large no mortality benefit was observed in the emergency postoperative patients. This was not true in the patients that were postoperative from elective surgery.

There was a similar rate of bleeding events in the rhAPC group regardless of their emergent or elected postoperative status.

RhAPC steady state concentrations were obtained in 326 patients. These steady state levels were divided in half, those at or below the median and those above the median.

The ranges went from 14 to 45 nanograms per ml and 45.1 to 391 nanograms per ml. The mortality, the number of patients with greater than or equal to one serious adverse event or greater than or equal to one serious adverse event during the infusion period was greater for patients with higher steady state levels than lower steady state levels.

This was, also, true for patients with serious bleeding events throughout the 28-day study period and during the infusion period.

Moving next to immunogenicity, combining the Phase II and III trials 942 patients received rhAPC. Of those 942 patients 370 patients had adequate blood samples to evaluate immunogenicity. This included a baseline sample and a sample on or after study day 12. The testing was done in a tiered manner. The first tier was a chemiluminescent binding assay. If this was positive it was followed by an inhibition chemiluminescent binding assay.

If that was positive an anti-APC neutralizing antibody test was performed. There are outstanding issues regarding the sensitivity, specificity and quantification of the assays. Based on this it is difficult to assess the true incidence of anti-APC antibodies.

Recognizing some limitations of these assays results were obtained in 370 patients. Of these 370 patients five had positive tier 1 testing determined by the

chemiluminescent binding assay. Two of these five patients had positive tier 2 inhibition tests. Neither of these two subjects tested positive for anti-APC neutralizing antibodies.

Of the two subjects with the anti-APC antibodies determined by a positive tier 2 inhibition test one was in the Phase II study and the other in the Phase III study. The subject in the Phase II study had no clinical sequelae.

The subject in the Phase III study developed superficial and deep venous thrombosis in the 28-day study period. This patient was alive at day 28 but on further follow-up this subject died on day 36 of multi-organ failure. There were no further reported thrombotic events.

The overall incidence of deep thrombophlebitis reported in the Phase III trial was 7 cases for an incidence of 0.4 percent.

Three of these cases occurred in the rhAPC treated patients. There was a higher overall rate of thrombotic events as presented by the sponsor.

In summary for the pediatric summary there were no controlled studies. No controlled studies were performed in the pediatric population to support efficacy, and there is a limited patient population from which to draw any conclusions.

In comparing pediatric to adult data drug effects

as reflected by the pharmacokinetics and pharmacodynamics were similar. However, the disease characteristics reflected by the type of infections and organisms and the type and number of organ failures are different.

Additionally, the mortality rate in the pediatric study was half of the rate observed in the adult Phase III trial. This low mortality rate is coupled with a similar rate of complications including deleting events and the occurrence of an intracranial hemorrhage.

This is important in assessing the benefit versus the risk in the pediatric population.

In summarizing the adult safety data it is important to reiterate that patients in this trial were selected to minimize the risk of bleeding. The major safety concern with rhAPC is the bleeding risk. This is reflected with a higher rate of bleeding adverse events during the infusion of 19 percent in the rhAPC-treated patients compared to 11 percent in the placebo group and an increased rate of serious bleeding events, 2 percent in the rhAPC-treated patients versus 1 percent in the placebo-treated patients.

In the Phase III trial four deaths attributed to bleeding occurred during the infusion period, all in the rhAPC-treated patients. Two of these were intracranial hemorrhages.

For rhAPC-treated patients this yields a rate of .2 percent for intracranial hemorrhages during the infusion period in the Phase III trial. In subsequent preliminary data submitted in late August open-labeled safety trials have enrolled 520 patients. Thirteen new intracranial hemorrhages have been reported, 8 occurring during the infusion period. This yields a rate for intracranial hemorrhages of 1.5 percent during the infusion period.

The sponsor has been assessing these cases on an ongoing basis, but these data, again, have not been formally reviewed by the agency.

One patients with anti-APC antibodies developed superficial and deep vein thrombi. This patient died at day 36 of multi-organ failure. Other than the increased risk of bleeding no other patterns of adverse events were observed when comparing the rhAPC-treated patients to the placebo-treated patients.

In conclusion, sepsis is a difficult condition in which to detect adverse events due to the large and varied number of events associated with sepsis itself. In evaluating products for the treatment of sepsis important safety events can easily be attributed to the underlying illness.

There is a clearly identified increased risk of bleeding in patients treated with rhAPC. Intracranial

hemorrhages were identified in only two patients treated with rhAPC in the Phase III trial.

New data suggest this may under-represent the actual rate. Additional intracranial hemorrhages may go undetected in situations where CT scan for practical reasons is not performed.

Thus, it is unclear what the true rate of intracranial hemorrhages may be. Other major bleeding events occurring in contained non-visible sites could be difficult to detect for the same reasons. Though major bleeding events were identified, the risk of these events remains somewhat uncertain.

Thank you.

DR. RELLER: We have heard the FDA presentation.

Are there questions from the Committee?

Dr. Fleming?

DR. FLEMING: I had one question of Dr.Forsyth and one of Dr. Lindblad. Let me start with Dr. Lindblad, but while I do could Dr. Forsyth raise the slide about functional status at day 28 while I am asking the question of Dr. Lindblad?

Dr. Lindblad, one of the key issues as we look at the lowest APACHE II group is this SAE bleeding. You noted there were 9 cases versus 0, and that is certainly going to be important as we are looking at benefit-to-risk.

Can you tell us the survival status of those nine?

DR. LINDBLAD: Actually I can look that up for you and give that up to you. I don't have that right at my fingertips.

DR. FLEMING: Okay, it would be helpful to get that.

Could we have that functional status slide? If we are having trouble digging it up, could we go to another question and then we will come back to my question?

DR. RELLER: Dr. Suffredini?

DR. SUFFREDINI: I wonder if Dr. Lindblad could address the issue of whether the changes that were made in the protocol in terms of part two in terms of the changes in malignancy, acute MI, acidosis, etc., were distributed equally across both the treatment and the placebo group?

DR. LINDBLAD: Could you repeat the question?

DR. SUFFREDINI: Sure, I will try one more time. Let me repeat the question? I am sorry. In terms of the changes that occurred in the protocol from part 1 to part 2 were the changes that occurred in terms of malignancy, acute MI, acidosis, etc., hypertension, were they equally distributed across the treatment and the placebo groups?

DR. FORSYTH: As far as I know they were distributed appropriately.

DR. SUFFREDINI: But we don't have formal data on

that?

DR. FORSYTH: No, we don't.

DR. ZWIGERMAN(?): We can dig up those final numbers. This is Bill Zwigerman, the Chief of the Branch. Yes, they were equally distributed between the two arms of the study but Dr. Forsyth pointed out on her slide that there were differences between the first and second half, if you will of the protocol.

DR. RELLER: Dr. Carcillo?

DR. CARCILLO: I have a question for Dr. Lindblad, please? Do you know if there were any children who were receiving activated protein C who died after 14 days in the pediatric ICU that were not included in your 10 percent mortality at 14 days?

DR. LINDBLAD: No, I don't know that. One of the difficulties with the pediatric study is the adult study was stopped early. The pediatric study was not finished. The initial submission included only 54 patients in that study. Subsequent data was provided and actually that I saw for the first time in the briefing document as well, too, so that it is an ongoing process. The final study report hasn't been finished. The sponsor may have some data to address that.

DR. RELLER: Let us come back to Dr. Fleming's question about the functional status for Dr. Forsyth.

DR. FLEMING: While the slide is being put back

up, let me compliment the designers of the trial for one very important feature; and that is the study was providing uniform follow-up of survival through day 28, and in some of the historical trials there had been debates as to whether 7 days or 14 days is enough follow-up, and what we saw was that in fact there were one-third additional deaths that occurred during that second 2-week interval and I think the informativeness of this study is greatly strengthened by the duration of 28 days, and yet even at 28 days I had done some hand calculations, and I was delighted to see this slide because they exactly bring out the hand calculations. Twenty-eight days is critically important in survival status, but there is more to the status than just that figure would indicate.

What we can see is, and what we focused on is the difference in the red, that there are 6.1 percent fewer deaths which numerically is a difference of 49 additional deaths in placebo and yet the green and the yellow groups there are those that are hospitalized and there are exactly 46 additional treatment patients in the hospital.

So, essentially what this translates into then is a 6.1 percent reduction in death, but of that 6.1 percent 5.1 percent are in the hospital.

So, it is not as though we are in essence increasing by 6.1 the percent of people who are home.

Essentially for the most part the prevented deaths are people who were in the hospital. Clearly it is better to be in the hospital than to be dead, and yet it is unclear exactly what this will translate into in terms of overall effect, and the reason this is important as well, and we will come back to this later on is that this study does meet the standard for strength of evidence for a positive study for a single positive study and that is of course, though on survival, and if you in essence though subtract off in some subjective sense the fact that you are hospitalized you could readily if you subtract off anything meaningful be moving to a level where this wouldn't be significant.

Clearly the study isn't remotely significant in the number of people who are alive out of the hospital because there is only a 1 percent difference.

Is there anything known about what the implications are, in essence that what we are doing really is keeping people alive but in the hospital what those implications are?

DR. SIEGEL: You noted that there had been calls for a study. I should say that really over the last 10 years while there have been calls in some cases for primary end points at 7 days and 14 days, in fact, there have been calls for 2-or-6-month follow-up for some of the reasons you mentioned and I think that some people have conceptualized

sepsis as a relatively acute event that you either die from or recover from, and this study would suggest, however, since only 10 percent of these patients I think were in hospital prior to entry to development of sepsis, 80 percent were at home, that in fact there is a substantial rate of chronic sequelae. I think the point is well taken. I don't have any data to indicate what will happen to those 5 percent of patients obviously. I think that is an interesting question that struck us as well in the analysis.

DR. RELLER: That was Dr. Siegel responding to Dr. Fleming's question.

Dr. Warren?

DR. WARREN; I had two questions relating to the first and the second half of the study. The first was did you analyze bleeding comparing the first and second half of the study? We saw there was a large difference in efficacy, but was the bleeding equivalent across the study and similarly because I guess there was a change in the way the drug was made. Were the antibody levels also different between the first and second half of the study because one might imagine that that would a sensitive way to pick up differences in glycosylation?

DR. LINDBLAD: I actually had looked at some of the bleeding differences between the first half and the second half and could not discern any differences between them, and

as far as the antibody levels, as I alluded to there are some issues with the assays that we are working out and the overall detection of the antibodies was so low that I don't think that that is going to be helpful for us at this point.

DR. RELLER: Dr. Rotello?

DR. ROTELLO: Two questions related to the scoring. APACHE II has been validated at the time of admission to ICU, and I was curious what the census of your patients when they had their APACHE II done at baseline were and was that coincident with the time of admission to the ICU, and No. 2, the APACHE split into two separate parts acute physiology and chronic health evaluation. Some of the criteria that changed in the second part of the study would have been patients who received points for chronic health evaluation. So, the same number of APACHE points could be weighted differently based on their proportion from chronic health evaluation versus acute score and would relate to a different mortality.

DR. SIEGEL: Let me comment on that? We tried actually to get a handle on the question of to what extent the APACHE was measured within the first 24 hours of ICU admission. I am not sure that exact information is available. I talked to the review staff and talked to the Lilly staff, and we may be able to get a better handle on that.

What we do know is that at the time they developed sepsis as I understand it only 10 percent of these patients were in the hospital. So, most of these patients are coming in septic, being admitted to the hospital and probably being admitted to the ICU relatively early in the course of having their APACHE done. It is probably, one would guess although I can't say with any degree of firmness that it is a relatively limited number of patients who had their assessment after being in the ICU for an extended period of time.

It is worth noting in this study as was pointed out in Dr. Forsyth's presentation and in virtually every other study we have seen and if the APACHE II or other risk measures that are similarly validated are measured at the time of study entry or within a window prior to study entry, the APACHE in this study did although no measure the way it was optimized which is measured at time of entry, did in fact serve as a powerful predictor of mortality with the 12 percent mortality in the low quartile and a 49 percent I think it was in the high quartile and graded values before this, and we have seen that in a number of other trials in which it has been used at entry, and so it may not be optimized for that, but it certainly is an important mortality predictor.

There is a couple of things I wanted to say, as

well for the FDA presentation regarding the APACHE and the issue of risk and regarding some of the Lilly comments in particular.

We agree with the comments by Lilly that these variations could have arisen by chance and that the study was under powered for subgroup analysis and as Dr. O'Fallon mentioned under powered for interaction analysis as well, and that doesn't mean of course that subgroup differences don't exist or interactions don't exist. It means unfortunately that it is hard to tell because if they exist they still might not be statistically significant, and the questions we are asking the Committee about this analysis are not at all should we conclude that an interaction exists or there is a problem. The questions are simply is there a strong enough suggestion and are the implications of potential interaction important enough that they should be addressed somehow by further studies in particular.

In that regard we look, you can look at the data, and that is what has been looked at, but when you look at it of course, when you look at subset analyses which have been perhaps appropriately criticized at various times in this meeting and at many meetings, is biological plausibility, prospectivity and strengthening consistency of the suggestion of an effect and to comment just quickly on each of those, on biological plausibility sepsis is an extremely

diverse syndrome.

People working in sepsis have been tackling on the fact that the underlying disease of the patients varies, the organ involved, the organism involved, the physiologic response involved varies and importantly you can integrate some of those factors and others into a severity risk. The severity risk has long been recognized as having the potential for being one of the more important factors and in the ACCP reprint that is in your folder, ACCP SCCM consensus reprint in which the definition for septic shock that was used was discussed there is an important recommendation that the newest terminology, quote, should be used with risk stratification or probability risk estimation techniques, and the rationale for that was that accurate identification of pretreatment risk can improve the position of evaluation of new therapies. Such risk estimation can also be useful in monitoring the utilization of new therapies and in refining the indications for specific treatments by identifying risk levels where certain therapies appear to be efficacious.

So, suffice it to say over the ensuring years of many trials and before many analyses have and many investigators have at least postulated that this could be an important interaction.

From a mechanistic point of view it is not hard to

postulate a couple of ways in which that can be important. If you have a benefit that is proportional to risk so that you lower mortality proportional to the risk by 4 percent if it starts at 40 and by 1 percent if it starts at 1, but you have a safety risk that is constant then that safety risk can overwhelm the benefit in low-risk patients and not in high-risk patients.

You could, also, have a different pathophysiology in low-risk patients than in high-risk patients. It could be a surrogate for other factors that indicate different drug effects.

As far as prospectivity and those things speak somewhat to the general idea of prospectivity it is worth noting in this trial that the covariates looked at and notably APACHE II were prespecified. There were many prespecified covariates in this trial.

We did ask the sponsor to rank order them. I think the APACHE was fourth or fifth. It was pretty high behind some involving protein C level and coagulopathy state which were, of course, also, prespecified for obvious reasons as potential important covariates.

As far as the strengthening consistency of the suggestion Lilly showed you some slides within that first APACHE quartile that suggest, I think they looked at SOFA scores, number of organ failures, and maybe IL-6 that

suggest that it looked like the higher risk groups were the groups where, that the lower risk groups, if anything had the most benefit or the higher risk groups had the most suggestion of a reverse effect and suggested that there is an inconsistency in the data there.

I am concerned about that sort of analysis. I think that you are talking about a group that has a relatively low total risk in the first quartile and that is fixed, and if you subdivide them by other measures, measures other than APACHE you can have unanticipated effects.

So, people who have high-risk because of organ failure are likely to have very few other risk points or they wouldn't still be in that APACHE or people who have low IL-6 levels but their organs are failing because you have to have organ failure to be in the trial might be more apt to have coagulopathies.

You get into some funny aberrancies. I don't know the latter is the case, but it certainly -- so, we have looked at that analysis subdividing APACHE quartile by APACHE, subdividing it into octiles, and it is worth noting there that the lowest octile showed 3.9 percent higher mortality on rhAPC with a relative risk of 1.32 and the second octile showed a 2.0 higher on rhAPC with a relative risk of 1.17. So, that suggests that within that there is a consistency in direction, and finally although a great

number of analyses were shown to suggest that that was not a consistent effect of low risk it is worth noting that as we look at the data several that we think are perhaps the most important to look at are confirmatory of a suggestion of a risk-related interaction.

Over the years of sepsis study shock and organ failure have been perhaps the most commonly, perhaps more recently with IL-6 touted predictors of possible interactions with the mortality effects and shock and organ failure were both very powerful predictors not only of mortality but also suggested in both cases larger treatment effects in the more severely affected than the less severely affected patients.

It has recently come to light in discussions with Lilly that shock interesting, you know on the one hand they showed cardiovascular SOFAs and we showed shock. Interestingly if you look at their slides the shock was actually a much better, shock within 6 hours was a much better predictor of risk level than, that is Page 41 of their slides, than cardiovascular SOFA which I guess was within 24 hours. Whether it is the time difference or something else I don't know, and we haven't yet fully reconciled why we see those differences.

So, I will just leave it at that, but I did want to put in some other perspectives, again not to suggest that

these subset analyses drive toward any conclusion but just to lay the background as to why we notwithstanding the issues they raised, why we think it is important to discuss whether they merit further study.

DR. RELLER: Two final questions, and then we will break for lunch.

Dr. Suffredini and then Dr. Lilly.

DR. SUFFREDINI: I wonder if Dr. Forsyth could address the issue. I guess I am concerned about your conclusion that the treatment was efficacious with laboratory evidence of DIC, and my concern is that the definition as used by the sponsor is certainly not robust in terms of the two out of four parameters that are used are really very common abnormalities that one would see in any patient that goes into ICU and certainly don't meet the criteria that most textbooks would use for DIC and what a practitioner would consider severe disseminated intravascular coagulation.

So, it is not surprising since there is not a discriminating factor DIC the definition used was so broad. It is really not DIC. It is an abnormality in coagulation perhaps, but that is really not DIC, and so, my concern is in terms of labeling or in terms of how the practitioner would look at this and use it in someone with profound DIC. I am not sure if the data exist to tell us that that would

be useful or not.

DR. FORSYTH: I totally agree with you and as far as the no standard definition of DIC we certainly understand that and this is the way that the sponsor has proposed to address the issue of DIC but I agree with you on that. That is an issue.

As far as labeling is concerned, we have been struggling with this issue.

DR. SIEGEL: We are going to take your advice, of course, on how we should address that in labeling, but this is not DIC. I think the slides say DIC but it is clear. It was called DIC in the trial criteria, but we agree it is not DIC, and the issues as will be brought out in the question are twofold.

One is is there a difference in treatment in patients who do have certain types of coagulopathy and not and there is not much data here to suggest that. The other is this is somehow a select patient population that has such a high incidence of coagulopathy that in some way we need to alert people that we don't know about the impact in patients who might not have all these abnormalities and we are seeking your expertise on that question.

As you heard for Lilly they looked at at least one other trial at the number of people who met these criteria and it was quite similar, and we have looked at the platelet

criteria and found it similar in other trials.

DR. RELLER: Thank you, Dr. Siegel.

Dr. Lilly, and then we will break for lunch. There will be additional discussion and just before lunch I want to point out a few things on the revised schedule.

DR. LILLY: Can you or can you not account for the excess mortality in the lowest APACHE quartile by the reported bleeding related SAEs?

DR. LINDBLAD: That gets into Dr. Fleming's question, I think, and of the nine serious adverse events four of them resulted in death in the 28-day study period. So, it doesn't entirely account for it.

DR. SIEGEL: I am not sure. It is very easy to address that sort of question. It is my perception and we have seen this in other ICU trials like if you are in the ICU on a ventilator, say and on pressor agents and you suddenly crash and you are septic and you suddenly crash and die the likelihood that someone is going to do a postmortem to see whether that death was related to an ICH or not is probably pretty small, and so I am not sure.

If ICHs for example were accounting for a few percent extra mortality you might pick them up in survivors but in patients who are critically ill I am not sure. I mean this has always been an issue even in the MI trials.

Within those who die it may be difficult to know

what the true incidence of serious or for that matter if they, even if their blood pressure dropped because of a sudden major hemorrhage internally it may not always be known I would think.

DR. RELLER: Thank you. It is time for lunch.

The public hearing we estimate will be approximately one-half hour. Since we are breaking for lunch late we will skip the afternoon break.

We will be back on schedule, and we will have continuous discussion and then addressing the questions.

For the Committee members there is a reserved table, if you are interested in the restaurant.

We will reconvene promptly at 2 o'clock.

Thank you.

(Thereupon, at 1 p.m., a recess was taken until 2 p.m., the same day.)

P R O C E E D I N G S [2:00 p.m.]

DR. RELLER: As people gather around the table and take their seats, I want to remind members of the advisory committee to speak naturally about six to eight inches from the microphone with the red circle on. If you are too far back, it encourages vibration and we are getting excellent audio help to try to minimize that so that we have clarity of the transmission of questions and comments and discussion.

We will open this afternoon's session with an open public -- comments in an open public hearing. I would remind the speakers that if there are any current or previous financial involvement of any kind with any firm whose products are presented now or compete with those products, that they appropriately would comment on that financial involvement.

Agenda Item: Open Public Hearing

Our first speaker this afternoon in the open public hearing is Dr. William Lyons, who will speak from the podium, as will the other speakers in this session.

Dr. Lyons.

DR. LYONS: Dr. Reller, members of the advisory committee, ladies and gentlemen, I am Dr. William Lyons, a surgeon from Falls Church, Virginia. I wish to present to this gathering quite a different view of sepsis and the

possibility of XIGRIS interacting with it. The view will be a lot more clinical than the statistical presentation that we have heard.

Now, I think this committee should be quite circumspect in their deliberations on the approval for this drug. I believe that there are many solid reasons why it should not approved. Now, in the first place, if XIGRIS is approved for sepsis, then it is going to be used in a great number of related entities, off label, so to speak. Immediately, one can see the possibilities for indiscriminate and excessive use.

Now, secondly, the medical establishment doesn't really understand sepsis. Take a person as prominent as John Mannick of Harvard Medical school. Only last month in The Journal of the American College of Surgeons he said that sepsis is this perplexing syndrome and he has been working on sepsis for about 20 years.

Kenneth Brigham from Vanderbilt, for example, 15 years ago, referred to the respiratory failure of sepsis as a complete mystery. I have seen nothing in the literature that he has gone back on that. Brochard and Abraham and Matthay in the past year have asked this question in publications. What is ARDS? Of course we know that is the lung failure that is part of sepsis.

Well, what is sepsis. Arthur Baue, a prolific but

respected surgical writer, only this past year said that it is neither a disease nor a syndrome. Well, for heaven's sake, what is it? Well, we can say this that there is no satisfactory definition for sepsis.

We used to think that sepsis meant to the public and to the physicians alike some sort of infection. Today, the definitions, if we have -- such as they are of sepsis, do not include infection even. So, sepsis is like pornography in a way. It is very hard to define but everybody thinks they know it when they see it.

So, I don't know, that is no basis for the development of a new drug, a specific drug for a so-called specific illness that we don't really understand. From a clinical standpoint, sepsis is basically a nosocomial problem and it refers to an inflammatory process of some kind throughout our body, following an episode of trauma or major surgery or severe infection.

Perhaps half of the cases have a significant infection. Dr. Porter, though, down at the University of Virginia says whether they are infected or not, they are going to follow the same clinical course. Of course, an awful lot of these patients have DIC, as you have heard, and, furthermore, they have a tendency to be very anemic and they often need transfusions, even in the absence of bleeding.

They accumulate a great deal of fluid in their lungs, for example, and in their body in general. Finally, they do have a rise in the pulmonary vascular resistance, due to the fluid in their lungs.

Now, may I have the first slide, please?

Those who haven't seen the clinical picture of sepsis, here is the typical picture here. You can see the infiltrates centrally located in both lungs and evenly distributed. The heart is small, so it is not a congenital heart disease. Those of you who can read x-rays can see that this patient is in respiratory failure. He has an endotracheal tube in place and he would die without this support.

He also has two subclavian catheters. You can see one coming up here and another one over here probably for dialysis, for example, and, of course, the electrocardiographic electrodes.

Next slide, please.

Now, here is a typical ICU case in severe sepsis. Notice how distended he is, how full of fluid this man is. He has gained 50 pounds in just a few days before this picture was taken. He is on the ventilator. He is in complete respiratory failure. You see he is strapped down. So, I think we can assume he has got ICU psychosis, probably from a diminished cerebral profusion. His thighs are big

and he has got the catheter in place and then a continuous IV.

May I have the next slide, please?

This is a patient, after discussing the problem with the doctor, who just couldn't quite convince him, maybe he couldn't convince himself what was going on with this patient. When he finished the discussion, then the patient's wife said, "But, Doctor, why does he look like the Michelin man?" Well, we learn a lot from our patients. That is why I developed that slide.

You can take the slide off, please.

Now, with regard to the generalized inflammation, what does XIGRIS do for the inflammation? Well, we have had other drugs like aspirin and ibuprofen used and they have known anti-inflammatory properties and, of course, they failed. The most powerful anti-inflammatory drug in the possession of the medical profession, cortisone, was tried some time back and it distinctly made the patients worse and increased the mortality rate.

Now, XIGRIS anti-inflammatory effect is basically unknown. It is not likely that it would even begin to approach steroids, for example, in effectiveness. XIGRIS is not an antibiotic for those cases that are infected. XIGRIS with its fibrinolytic properties is sure to complicate the care of people with sepsis and DIC, for example.

XIGRIS is not any kind of a hematinic or marrow stimulant that would improve the blood count of these people who become so anemic and often need transfusions. It is not a diuretic. It will not help the patient rid himself of the large amount of fluid that he has in his system. It does nothing, of course, to reduce the pulmonary vascular resistance and the pulmonary hypertension that so complicates the management of the blood pressure in these people with severe sepsis.

It would seem to me in going over these details that XIGRIS has very little going for it in its own right. It is a pity, too, because of the -- sepsis patients belong to a group of people in general in whom we expect recovery, the younger people in trauma and that sort of thing. So, it is a pity that we have no particular drug.

The John Mannick that I mentioned in the first part of the talk says that he -- he said that drugs are not going to be the answer and that prevention or prophylaxis is the way to control sepsis. Now, I personally think that the statistics that we have heard today are not particularly impressive.

What we have is a 6 percent reduction in the mortality rate from 31 let's say to 35. Manipulating this statistic is not going to make it any better. That is a 6 percent reduction in mortality and I submit that this is not

a particularly impressive clinical number. The cohort recruited by Lilly would seem to be not as sick as the patients that usually command our serious attention in the ICU and in surgery, with a cohort control that had a mortality rate of what, 31 percent.

In general, these patients with serious sepsis have more mortality rates running much higher than that. There is no doubt that we have a very serious clinical public health problem here. There were 225,000 people a year dying of sepsis. You can see that the mortality of cancer of the breast, cancer of the prostate, AIDS and automobile accidents together do not equal the mortality rate from sepsis.

We actually have, in my opinion, a public health crisis with sepsis. Now, I think from concept to application to cost, and oh, my Lord, the cost, that XIGRIS is an unsound drug and I think I would recommend that its approval be denied.

Dr. Dellinger from Rush Medical School is quoted as having said that he knows of no academic physician who would not recommend that XIGRIS be approved. But, you know, that is part of the problem. Academia has had this problem under their aegis for the last 25 years and here we are in 2001 with no specific treatment for sepsis.

I submit that academia is in consternation over

this and they are very anxious to have any kind of a new drug to try for awhile. I submit that this is not a satisfactory basis for approving a drug.

Dr. Reller.

DR. RELLER: Thank you, Dr. Lyons.

Our next speaker in the public hearing is Edward Wiginton.

MR. WIGINTON: Hello. My name is Ed Wiginton. I am a board member with the Meningitis Foundation of America and I want to thank the panel for their attention of sepsis and for the opportunity to speak before you today on behalf of the Meningitis Foundation of America.

My family was robbed of our son, Jason, by meningitis and the subsequent onset of sepsis. I have come to learn that sepsis moves quickly and knows no mercy. Jason was a happy, healthy, 14 year old boy in May 1998. He loved his younger twin brothers, the Detroit Red Wings, WWF wrestling, running track and was looking forward to starting his first summer job very soon.

One day after school he came home with what appeared to be a normal headache and flu. Nothing could have been further from the truth. The next morning, Jason's symptoms worsened. In addition to the high fever, he was now starting to bruise and develop a rash. We knew something was terribly wrong. My wife rushed Jason to the

doctor's office and the time they arrived, new bruises were forming by the second.

The doctor recognized that the infection was taking over his body and rushed him to the hospital. From that point on, it went down hill fast. The doctors said that Jason had Meningococcal Septicemia. Due to the severity, the medical team decided to transport our son to a children's hospital in Detroit. Jason didn't even survive the transfer.

I can't begin to tell you what it is like to watch your child literally degenerate before your eyes and not be able to save him. Now I know first hand the devastation sepsis brings. I also know that decades have gone by without any new treatments and that physicians and families have little hope.

My wife and I have dedicated our lives to trying to prevent other parents from having to go through the ordeal we did and I am asking for your help.

This terrible disease affects hundreds of families everyday. Please do not let a day be wasted in an attempt to make new therapies, rather, new hope, available to fathers like me.

Thank you.

DR. RELLER: Thank you, Mr. Wiginton.

Our next speaker is Alvin Lever with the American

College of Chest Physicians. Mr. Lever.

MR. LEVER: Thank you. I am pleased to be able to present before the FDA. First, as the executive vice president of American College of Chest Physicians, I do want to disclose that the college does receive unrestricted educational grants from Eli Lilly and our Chest Foundation also receives grants from the Lilly Foundation.

I also want to disclose, though, that I have not been paid, received any honorarium for this presentation. So, I wanted to make that clear.

I want to do two things. First of all, following our prior speaker, to give a very short personal story. My father died in an ICU of severe sepsis, multi-organ failure, 25 years ago. In that 25 years, we have not seen any increase or any improvement in decreasing the mortality from this dreaded problem.

There is a concern both of mine, as well as most of the members of the college. The American College of Chest Physicians has been long involved in this issue. I worked with Dr. Roger Bone in the development of the consensus statement that we did distribute to everybody as attachments to our documentation. It is an important issue. The statistics show for themselves and I will just say for myself that had I seen the statistics that were delivered this morning and my father presented today and I was asked

for informed consent, I would definitely give it based on the benefit-to-risk ratios that I was demonstrated with today.

So, I think from that standpoint on a personal level, I would like to see this move forward. I think we need some solutions. You all know that we publish the journal Chest. We are very active in the education on sepsis and all critical care issues and had developed a consensus statement together with the Society of Critical Care Medicine.

It is also important to note that it is an ongoing problem that is constantly addressed in all of our meetings and this is as it appears one of the first opportunities to find something that might work. It is, therefore, my pleasure, though, to introduce Dr. Curtis Sessler, who is a past board member of our Board of Regents, on our education committee. He is a professor of medicine at the Virginia Commonwealth, medical director of critical care at the Medical College of Virginia, to speak on behalf of the membership and the leadership of the college.

Thank you.

DR. SESSLER: Good afternoon. I would lie to thank the FDA for the opportunity to offer a few comments on behalf of the membership of the American College of Chest Physicians. Sepsis is bad. Thank you.

You are supposed to laugh. Seriously, experts now estimate that 750,000 people in the United States will develop severe sepsis annually. These experts also estimate that more than 200,000 individuals will die as a result of this illness. It is considered to be the most common cause of death in non-cardiac ICUs.

Further, it is anticipated that by the end of the decade more than one million Americans will develop severe sepsis each year. The basic components of our management of severe sepsis have not really changed appreciably in many years. Management typically includes elimination of the infecting organism, shock resuscitation and support therapy for failing organs.

As a practicing critical care specialist for the past 16 years, I have seen my share of folks with severe sepsis and septic shock. Unfortunately, like many other clinicians, I have cared for numerous patients, who have succumbed to this illness, despite aggressive management with all available interventions and successful treatment of the underlying infection.

We know that considerable time and resources have been invested over the past several decades in search for new agents to modify the inflammatory response to infection that is thought to contribute greatly to the development of shock and organ failure. Clinical trials testing novel

agents have uniformly had negative results in reducing sepsis-related mortality.

Many explanations have been offered for this apparent lack of efficacy. These include a variety of study design issues, insufficient sample size and the perhaps overly optimistic rationale that blocking the effects of a single pro-inflammatory cytokine will be sufficient. Recombinant human APC represents the first agent and new class of drugs that may improve the outcome of severe sepsis by altering its complex physiology at several levels. This combination of anti-inflammatory, anticoagulant and pro-fibrinolytic effects at the microvascular level may be important to ameliorate shock and organ dysfunction; thereby, improving the likelihood of survival.

I recently spoke not far from here on the topic of septic shock at the Washington Area Critical Care Society annual meeting. I started the discussion with a particular case presentation that I always use when I talk about septic shock, of a gentleman who developed septic shock several weeks after having undergone abdominal surgery.

I found this case to be particularly instructive for a number of different reasons. First, it is an absolutely classic presentation for septic shock with all the manifestations outlined in the definitions put forth by the consensus committee from the ACCP and the SECM.

Secondly, the patient had a good outcome, recovered fully and, third, the case is actually one of the first published cases of hospital acquired sepsis. It was published in the journal Archives of Internal Medicine in 1951. Yet, the management could very nearly pass for current day management.

One of the big exceptions was the antibiotic used was something called aureomycin. Never heard of it. But unfortunately this case does illustrate our relative lack of significant progress in sepsis management, despite the passage of in this case half a century.

In closing, the American College of Chest Physicians salutes the many scientists and clinical investigators in their ongoing search for new agents and techniques to improve outcomes of our patients, who have this common and devastating disorder. We also recognize the importance and support the role of a thorough review of the evidence for safety and efficacy so we can best use these new products.

Thank you.

DR. RELLER: Thank you, Dr. Sessler.

Our last presenter in this session is Thomas Smirniotopoulos. Dr. Smirniotopoulos.

DR. SMIRNIOTOPOULOS: Thank you for allowing me to speak. I am a practicing pulmonologist and critical care

physician for 15 years in Alexandria. I also am a consultant to the U.S. Department of State for their pulmonary clinic, which I have done for that time.

My experience with sepsis dates back at least that length of time and my experience has been similar to what you just heard, that we have a difficult time managing many patients with sepsis. The mortality is very high. As you heard Dr. Lyons speak, sometimes we do see mortality as high as 50 percent. Lately, I think, the mortality is a little bit lower for our patients.

But we are constantly looking for something else to treat these people because we really are using everything that we have, every bit of our armamentarium, which we have to use we use on patients. We see patients continually deteriorating, especially when they develop multi-organ dysfunction syndrome.

We know that we are losing the battle. This new drug, activated protein C, only became available for my use after the September 11th terrorist attack, when I took care of a smoke inhalation victim from the Pentagon. This gentleman, who seemed to have simply laryngeal edema from smoke inhalation was doing fairly well and we were ready to extubate him.

However, on about the fourth day, he suddenly required 60 percent oxygen, 8 centimeters of PEET(?) and was

developing diffuse ground glass interstitial infiltrates. Because I had been aware, watching this drug, waiting for it to come about, I was able to get this drug on compassionate use basis for this patient.

I have to say that I am very thankful to have been able to get this drug for this patient. He definitely benefited from this drug. I don't want to have to go through the red tape in the future that I had to go through for this patient to get this drug. I want to see this drug available. I agree with other speakers that we need to have some restraint on how this drug is used.

In our institution, we have implemented a protocol that is going to restrict the use. It is going to fairly well mimic the protocol that was used for the investigational study. Our belief is that this drug will be useful. It will be used for patients who have severe sepsis, who are going into organ failure. And I believe that it will benefit many of them. I am sure that not all of them will survive simply because of this drug.

But anything else that we can have that will help us to manage these severely ill patients, I think we have to have. I can't possibly imagine any reason why this drug shouldn't be made available. I hope it will be made available very soon. It was on September 11th that this panel, I believe, was originally going to convene and, of

course, was cancelled, as have many of the other plans of many Americans been cancelled from that date.

But, hopefully, one thing that we can do here today is we can move forward with at least one weapon that we have to fight a serious problem in this country.

Thank you.

Agenda Item: Charge to the Committee, Introductions to Questions

DR. RELLER: The open public hearing is now closed and we turn to the questions and discussion. To aid in this process, I would remind the committee that our charge is not to approve or not approve anything, but rather to give our advice to the Agency in their responsibilities, including we will have some votes, but other portions, where there will be discussion that the content of the discussion as captured in the recording will be available for the Agency's consideration.

So, before we restrict the discussion to the committee members and take the votes, I want to make sure if there be any leftover questions from earlier or comments, that we get them made succinctly because thereafter things will move along better if we have the discussion within the committee itself.

Any questions to either FDA or to Lilly from committee members that we did not get to this morning? Yes,

Dr. Archer.

DR. ARCHER: I had a question. I am not sure whether anybody will be able answer it or not. I just wanted to get an idea about how many sites were involved in the trial, approximately how many patients were enrolled into the protocol per site and if there is any idea of the patients that were available for entry, how many were approximately not entered into it? About what percentage of the patients with sepsis at the institutions contributing patients actually got entered into the trial?

Is there any way of knowing that data?

DR. RELLER: Dr. Macias.

DR. MACIAS: Thank you.

There were 165 sites that participated. The number of patients enrolled per site obviously varied and I think this morning we showed you an analysis by the number -- the outcome by the number of sites, whether the sites enrolled greater than 25, greater than 20. So, it is really quite variable.

There were approximately 4,300 patients screened to enroll approximately 800, of which -- I am sorry -- 4,300 screened to enroll the 1,700 and some that were eventually randomized, of which 1,690 received drugs.

DR. RELLER: Dr. Ramirez.

DR. RAMIREZ: Just for my clarification, I

understand that when the protocol was revised, the objective of the company was to decrease the number of patients with the syndrome that were not due to sepsis and the other idea was to decrease the number of patients that may have complications.

I still don't know -- what was the rationale to apply to now restrict the population just to organ disease function in the first 24 hours? What was the rationale to not to enroll patients -- the idea is for four days.

DR. MACIAS: Just to answer your question very briefly and to make a point of clarification from this morning's session, this is the cumulative mortality over time that was presented during the FDA document for all 1,690 patients. This point in time is the point at which the first patient was enrolled under the amendment and in October was the point at which the first DSMB meeting was conducted.

Lilly signed off on the protocol in March. So, Lilly was completely unaware of any of the data -- I just wanted to take a moment and assure you of that. We had not access to the treatment codes and were completely unaware of the data as we amended the protocol. It took us a few months to get the amendment set in place and then we signed off on the amendment on March 2nd.

With respect to limiting the duration of organ

failure, the intent of the protocol had always been to limit the duration of organ failure to 24 hours. That was just not included in the original version of the protocol and it followed recommendations that had come out of the ibuprofen studies that Dr. Bernard had run, where at the time you meet inclusion criteria, the organ failure can be no more than 24 hours old and it just wasn't included in the original protocol. But that had always been the intent.

DR. RAMIREZ: But still the question is what is the rationale? I mean, are you thinking that if you go beyond 48 hours -- because in your comments, you mention that there was a question addressed to you regarding there was a need to indicate this drug only for 24, 48 hours, and you mentioned, well, I don't think that is going to be necessary because this drug is going to work even if the patient is at 48, 72 or four or five days.

Still, my question is what was the rationale of the company to put this exclusive criteria?

DR. MACIAS: I am going to ask Dr. Bernard to answer that question for us.

DR. BERNARD: Yes. In helping to coordinate the study and interpret the inclusion criteria, the kinds of problems we would run into would be a patient who had, say, blunt trauma to the chest in a car accident and for a week is on a ventilator and only a week later did they finally

have fever and a white count. Now they meet in the 24 hour window, they meet the criteria for the study. That is not a sepsis-induced organ failure, but, yet, technically that patient under the original criteria could meet study criteria.

Do you follow what I am saying?

DR. RAMIREZ: Yes.

DR. BERNARD: So, we wanted to make sure that it was the organ failures which started the clock for getting the patient in the study, not temperature or heart rate or the surface criteria.

DR. RELLER: Dr. Wald.

DR. WALD: I wondered, did you do any separate analysis of the 970 patients that were enrolled after the amendment, either with regard to that first quartile APACHE outcome or with regard to the long term outcome at 28 days regarding home, hospital, ICU?

DR. MACIAS: We actually did look at the treatment by APACHE for patients enrolled under the amendment. In four patients enrolled under the amendment, lower mortality is observed in the Drotrecogin Alfa activated group for patients enrolled under the amended protocol.

If you would like the exact numbers, we can calculate those for you.

DR. WALD: Then with regard to the overall

outcome, was that any different than for the entire group? You know, one might expect that if you were eliminating some of the patients with chronic illness, that, in fact, their 28 day outcome might have been improved, compared to placebo.

DR. MACIAS: You mean, in terms of disposition, whether they were home?

DR. WALD: Yes.

DR. MACIAS: I don't think we did that, but I think we can -- excuse me.

DR. RELLER: We will let Dr. Macias and his colleagues get that together. Give them a few minutes.

Then we will go to other questions. Yes?

DR. EICHACKER: Yes. I guess I can direct this to the FDA, but in your analysis of the data, is there a way to differentiate -- if the drug, the batch of drug was changed at the same time that the exclusion criteria were changed, is it possible to differentiate a drug effect versus an exclusion effect for the differences between the first half of the study and the second half of the study?

DR. SIEGEL: It was actually the new batches of drug were introduced at a somewhat different time at each clinical center. So, there is no single point in time, unlike, say, the protocol amendments, where they switched over from old drug to new drug. It depended on stocks and

supplies at each center.

We made some efforts to try to, for example, identify the precise placebo group that was being given at any given center alongside, when they were getting the second batch of drugs and the company had some difficulty in analyzing data in that manner.

So, largely, our analyses are based on specific points in time when switchover occurred. I think the basic answer to the best of our ability to detect is that although it occurred over a period of time, the switchover in drug occurred at a point close enough in time to the change in the protocol that it would be hard to differentiate, you know, to identify patients who had experienced one change but not the other patient -- change, the numbers would so small as to not tell you anything.

So, what we wound up doing, just as looking at all the protocol changes, to see what implications they might have had and what they did have, we looked at drug changes and I think it came out in earlier conversations. Dr. Johnson can speak to this in more detail, but I do want to state and I know Lilly stated something similar, that we requested extensive types of analysis and testing.

I should note in a complex biological, you can't be sure in any lab testing that you fully know the physical, chemical nature of the product. We have seen changes occur

in behavior of products that are beyond our ability to detect in physical, chemical characterization, but with that said, this product was rather extensively looked at and we were unable to detect any changes attributable to the development of the new master cell bank.

DR. RELLER: Dr. Macias.

DR. MACIAS: We don't have the specific analysis, but we are running it for you right now and will give you the patient disposition for all patients enrolled under the amended protocol in a few minutes.

DR. RELLER: Dr. Macias, if you can work out of another window, are there any things that -- questions that were asked before that you think were not adequately addressed earlier. Then we will come back to the specific issue that is being worked on.

DR. MACIAS: I would like to make one quick question, just to reiterate with the timing of the amendment that we clearly were unaware of any of the data and that the integrity of the study is absolutely intact. You can bring this slide up.

Then the other comment that I wanted to make dealt with the survival benefit in patients with less disease severity and we have looked at a whole host, as we have talked about earlier today, of measures of disease severity. The point of discussion from the Agency side tends to focus

on these three up here. Yet, there are a whole host of them down here.

I just wanted to ask Dr. Mitchell Levy if he just wanted to make one brief comment about his interpretation of this particular treatment by disease severity analysis.

DR. LEVY: Well, I think what you see in terms of the problems and issues that have come up around the APACHE II score illustrates exactly why most clinicians don't use the APACHE II score in practice. The APACHE II score was established to relate to the severity and mortality prediction on the first day of the ICU and after that first day, it has not been validated and may not even be helpful.

So, if what you are doing is looking for patient population of low severity or prediction to survive, then, in fact, APACHE II score may not be -- a low APACHE II score may not be all that helpful. If you look at the subgroup of that APACHE II score, two-thirds of that group have a low IL6 level, which by another subgroup, in fact, had a survival benefit and a third had more than three organs down.

So, I don't think any critical care clinician would look at a patient with three organs down and say that that patient has a likelihood, a good likelihood, of survival. That is why I question the value of a subgroup analysis that looks at the first quartile of APACHE II score

that is not calculated on the first ICU admission day.

DR. ARCHER: Can I ask one of the statisticians -- I am an statistical idiot -- these things cross one of these confidence intervals. What can we say about those intervals and that data?

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: Well, we certainly recognize that they cross one and they never made any point of the fact that they crossed one or didn't cross one. The point is that the point estimators, the little diamonds, are all to the left side of the one and many of them are right inside the confidence interval for the overall effect.

This is the worst of their several slides of this type. I basically like this method of analysis and prefer that to their claims --

DR. ARCHER: So, that is relevant then.

DR. O'FALLON: So, I think this is a relevant slide.

DR. ARCHER: All right. Thank you.

DR. RELLER: Dr. Bernard.

DR. BERNARD: I just wanted to make one comment about the operationalization of APACHE. From a clinical trialist perspective, we have been collecting APACHE scores for years. It is to try to show whether or not the groups are well-matched at baseline. That is the main purpose.

But as I have thought about how you might go about using this in clinical practice, it gets very, very difficult. The APACHE window is a moving window in these studies. So, if you look at the APACHE score today in a patient, it may be different than tomorrow. It may even be different in a couple of hours. So, this is critical in trying to give some guidance to the clinician, who is trying to figure out when to use this drug and when not to use the drug.

Are they really supposed to calculate in the package score on a moving window and mae some sense out of that because, of course, the study wasn't exactly done that way? So, just to even think about how you would design a clinical trial that would look at just this low APACHE score, well, what part of the course would you look at them? And what would you do if their score changed during the time that they were on the study, which will happen, of course?

So, this is a very difficult process to work through and think about how you would operationalize something that involved an APACHE score as part of the evaluation for treatment.

DR. RELLER: Dr. Siegel, you had something you wanted to say.

DR. SIEGEL: Just a comment on a couple of those comments. If I could refer you -- I don't know how easy it

is to pull up the slides, but Lilly presented three slides on page 33 and 34 of their presentation of various -- their Slide No. 66, 67 and 68, that were all of those analyses that you just saw in terms of relative risk, based on what they term disease severity measures.

These three slides differ from that other slide in the way they are ordered. They show low and high risk, but most importantly, they also show the mortality rate. If you would look here at the placebo mortality rate in the first quartile of APACHE, it is 12 percent. There is not a single one of these predictors that identify the population anywhere close to that low a mortality, and particularly a population of that size; in fact, none even I think on any of the three slides.

If we could go to the next slide, you will see looking down the placebo column, that the lowest number there is 21 percent for one organ failure and the next slide, the lowest number there is 22 percent on the IL6. Again, that 12 percent on APACHE.

So, I think that APACHE was -- whether or not you think it is validated, APACHE was and it has been in every trial it has been used in, a very powerful predictor of mortality risk and identifier of low risk patients far better than any of these others.

Secondly, I would just take a little bit of

exception at the notion that shock and organ failure were kind of cherry picked among the huge number of severity measures of those that seem to show this effect. I mean, obviously, there are some improved. There are others that could have and that didn't.

I would ask the committee to consider, though, they are not all of the same significance. Whether, for example, hepatic organ failure score of low versus high is as important as some of the others, those are, suffice to say, maybe not the only ones, but among -- organ failure and sepsis and shock have been among those most commonly and most frequently discussed and hypothesized as indicators of both outcome and treatment impact.

Yes, it is correct that they fall on the left side of the line. However, it is also correct that in the case of -- if we can go back a slide -- I don't know if that is possible, but in the case of one organ failure and we will talk about 19 1/2 versus 21.2 percent mortality, that, in fact, for both organ failure and shock, there is a supportive suggestion of a possible interaction.

DR. RELLER: Dr. Fleming.

DR. FLEMING: There are some really critically key issues here. Obviously, statistical interpretation is critical in these. I had assumed that since there are specific questions here that I would give my comments then,

but would you prefer to get into this now because the sponsor and Dr. Siegel have jumped in in their interpretation?

DR. RELLER: Well, we definitely want to systematically go through all the questions and I would prefer to have the discussion in that context. But what we wanted to make sure that we got the comments from the persons who are not going to be voting out because once we get to the committee members, then to go back and forth, it just chews up a lot of time.

So, if there is something you want to ask of Lilly or CBER, now would be a good time. Otherwise, for your views and discussions, during the discussion.

DR. FLEMING: I will be delighted to follow your recommendation. I think you are right. Let's discuss them in the context of the question.

DR. RELLER: Okay. Please, go ahead, Dr. Suffredini.

DR. SUFFREDINI: If Dr. Macias could possibly address their role in the two studies and in the amendment summary, investigative sites had to contact a Vanderbilt coordinating center for questions about patient eligibility. And I wonder if you could clarify what that means in terms of from a practical point of view what are the guidelines that are being used to tell the investigator that, yes, they

are eligible or they are not eligible.

DR. MACIAS: I will as Dr. Bernard to address that since he ran the coordinating center.

DR. BERNARD: There are a whole host of imponderables as you know, Tony, in critically ill patients, surgical patients, emergency admissions, where you can't deal with all the potential bleeding risks in the inclusions and exclusion criteria. So, when patients -- when clinical sites had questions about whether a patient was at an excess bleeding risk, they would call us and discuss it.

Many times it had to do with numbers, like what the pro-time was right now versus what it was before two units of fresh frozen plasma. We have all those guidelines written and we have submitted those to provide some guidance as to whether or not the patients were too far out on the coagulation cascade to be safe to be put in the study or if they were too close to surgical procedures or trauma and so forth.

DR. SUFFREDINI:

I guess the concern I would have or it does bring up the question in terms of the subjective nature of this, which is a requirement in terms of is this person eligible or not in terms of applicability to a more general population? How difficult will that be in terms of determining whether someone because of your instincts or

because of your subjectivity is eligible to receive the drug and to get benefit from it or not.

DR. BERNARD: Well, that is all I can tell you is that the exclusion criteria were the ones we were focusing on, not the inclusion criteria. There is some interpretation of the window. It is not that it is not objective. It is objective. But the time window is a problematic feature of all of these sepsis trials, as you know. You have been involved in many of them.

But it was more just trying to clarify the bleeding risk criteria for the sites and we had this written-in guidelines that we have submitted.

DR. RELLER: Dr. Munford, you had your hand up earlier.

DR. MUNFORD: Yes. Could we see the cumulative 28 day mortality over time figure again, please?

DR. MACIAS: Absolutely.

DR. MUNFORD: While he is producing that, this is a familiar graph and so the point that perplexes me is the following. After the amendment of the protocol and the beginning of the use of the new formulation of the drug, the outcome was clearly different. Whereas, the drug was not efficacious during the first part of this trial, which one might consider the first trial, then it did become efficacious or seemed to be efficacious in the second trial,

but not for awhile.

So, beginning about the first of the year of 2000, they drug separated dramatically and progressively and I think the figure actually seems to underrepresent the efficacy of the drug, which must have been even better in order to produce those cumulative results.

The point that worries me is why did this happen. I mean, we are told that there is not a substantial difference between the product that is being used and we are told that there are subtle differences between the patient populations and who is being enrolled and so forth. But all of the sudden, something striking happened and if that had not happened, we would not be here.

My reservation is how do I know that the drug I get to give my patient is going to be the same -- have the same result that is seen in the last six months of the trial and not the result that was seen prior to that? Is there some way that we can be reassured about this? I guess that is more of a comment than a question, but if either FDA or the company has an answer, I would appreciate it.

DR. MACIAS: Dr. Munford, if I could answer the question or at least attempt to answer the question to your satisfaction, I will take the next slide, please. The way that we have tried to sort out whether or not there was an amendment of fact, was really to look at sites that enrolled

under the original and the amendment, to control for the site effect.

As we stated earlier in the presentation, this is the point in time when the first patient was enrolled under the amended protocol and the last patient was enrolled under the original protocol. During this time period, this month in here, there was kind of the transition phase. I think as we look at these data, we clearly believe that there is a treatment benefit that is evident early in the course of the study before the protocol was ever amended or before there was a change in the CT material from the BDS2 to the BDS2+ material.

At this point in time, now all patients have been enrolled under the original protocol. The curves stay relatively flat, maybe float around a little bit and then continue to separate, but if you drew the line over the course of the entire trial, this is what you would see and there is a gradual decline in the placebo mortality over time. So, I think these data, if you control for the side effect, I think these data do allow you to draw conclusions that there really was a treatment benefit prior to the amendment or prior to the change.

DR. MUNFORD: I am sorry to be thick here, but what is the difference between that figure and the previous one, which --

DR. MACIAS: You can go back to the slide that is up there currently. Just leave it here. We are quite adaptive. This slide shows --

DR. MUNFORD: But you like this one better.

DR. MACIAS: This slide shows the sites that participated both under the original version of the protocol and the amended -- and this is basically a hundred of the 165 sites, but they enrolled almost 1,500 of the 1,690 patients. This allows us to try to -- at least try to attempt to control for side effect, so that we can look to see what the sites did when they were participating under the original and then what they did when they were participating under the amendment.

That is the difference, between --

DR. MUNFORD: But I guess part of my problem is that I would -- my hospital would not have been a chosen site for this study as a big academic city hospital, right?

DR. MACIAS: Why not?

DR. MUNFORD: Well, I don't think you have very many of those in the trial.

DR. MACIAS: No. There were quite a few academic medical centers in the trial.

DR. RELLER: Okay. Now, we have a line up patiently, Dr. Cross, Dr. Murray and then Dr. O'Fallon.

DR. CROSS: I wanted to talk about that figure

that just disappeared.

DR. RELLER: `About this figure, Alan? We will reverse the orders.

Dr. Murray is about this figure and then Dr. O'Fallon.

DR. MURRAY: I was just going to comment that the comment was made that the drug was phased in slowly at several sites, which would even further support Bob's idea that it took a few months for the more active compound to be used at enough sites for the curves to differentiate themselves more from each other. So, it is just a little disconcerting.

Has this compound been evaluated in animals to the extent that the original product was? I heard about in vitro and all sorts of analytical aspects of it, but it was also looked at in the animal models?

DR. MACIAS: Animal models of --

DR. MURRAY: Whatever the original compound -- however it was evolved -- evaluated.

DR. MACIAS: Excuse me for one second.

The BDS2+ material did not go through the same preclinical animal toxicology studies that the original material did.

DR. MURRAY: Weren't there some animal efficacy studies that --

DR. MACIAS: No. I will note, though, that pretty much by the end of August/September, all of the sites had been converted over. We can check that, but that is my memory, that by this point in time all sites are enrolling BDS+ patients and the curve stays still relatively flat.

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: I am glad to see that being a statistician is contagious here. So, we are getting some help.

This type of figure is notoriously very variable early on, where the denominators are like 1 and 2 and 3 early on. They should be very stable later on. So, the fact that the green line is still decreasing, even though we are well into a situation where if the rates were constant, we should have gotten to a stable level, I think, is the point that is being raised so that the actual efficacy of the drug seems to be improving to overwhelm the circumstances earlier in the thing.

I think that is the issue that is being raised here. Why do we not see a steady state flat line? Let's assume there is a difference between the white line and the green line. Why is the green line still decreasing?

DR. MACIAS: I think actually Dr. O'Fallon, you would see the general trend involved. No? The general trend for the placebo population is to also fall.

DR. RELLER: This we will come to in the committee discussion because what we will be -- after we get everything out on the table, then we want to hear how the committee members, the consultants, the guests, how they put this altogether. That is what we are after.

Dr. Cross.

DR. CROSS: I would like to ask either Dr. Forsythe or Dr. Siegel for some help on the material that was passed out to us earlier, which has Kaplan-Meyer(?) plots of the pre-amendment and post-amendment survival. It looks as if under the original Kaplan-Meyer process on page 46 of the handout, that is almost superimposable; whereas, there is a difference with the amendment. Yet, in the slide presentation, looking at the sensitivity analysis, which is the patients on pre-amendment not eligible under the post-amendment, looking at the difference between those two Kaplan-Meyer plots, I would have expected that those who were -- who did not meet the new criteria, would have had a higher mortality. But that was not the case.

I was just wondering how you can reconcile your sensitivity analysis with the results you presented in those two Kaplan-Meyers plots?

DR. SIEGEL: Well, the data speak for themselves. How to reconcile them, of course, is entirely speculative. The data in the -- I am not fully sure I understand the

question. In terms of the sensitivity analysis in which we looked at the patients, who would have been excluded under the new protocol, the patients who would have been included under the new protocol, which is the large majority of them, showed a relative risk of .96. The overall relative risk before then was 28 percent versus 30 percent mortality or relative risk.

I am not going to calculate it, but that is why the Kaplan-Meyer looks so similar. You are looking at reaching at the end of Study 28 versus 30 percent mortality. Looking at the specific -- I think if I understand your question, the answer is that this analysis does not provide insight, if you are asking me to reconcile these, as to why these changes occurred, which is to say if you look at the group that was eligible in -- would have been eligible in the second half, if you look at them in the first half, the relative risk is .96, but in the second half, the relative risk is very low in that group and this does not -- so, it doesn't suggest that the entry criteria, at least based on this data analysis, account for the differences.

But if you are asking me how I account for them, I don't have an answer to that.

DR. RELLER: Dr. Fleming and then Dr. Chesney.

DR. FLEMING: Just a quick comment on this. There are two very important ways of looking at these data. Dr.

Siegel earlier called our attention to looking at the original patients, splitting them out by those that would still have been eligible under the refinement and those that wouldn't. Those that wouldn't, as you were pointing out, still seemed to show benefit.

This is looking at a different issue on page 46 of the briefing document. This is looking at, if I am interpreting right, the original cohort and then the subsequent cohort. It clearly shows a time effect, but as Dr. Siegel would say, not a time effect that is so simply explained by the change in the eligibility criteria.

So, we are left with a very substantial change that at this point has not been explained.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: This question is for the FDA. On page 3 of your presentation, the middle right hand slide, 'Serious bleeding events during the infusion period is very impressive." I probably should remember from everything we have heard and read what those serious bleeding effects were like in the post-infusion period.

Was there as striking a difference?

DR. LINDBLAD: The reason I focused on the infusion period is because I thought it was most relevant to the time frame of when the drug was effective or active, at least. There was continued bleeding events in both the

placebo group and the treated groups past the infusion period, but they were fairly well balanced between the two groups. I think the overall numbers added 12 patients in one and 13 in the other so that the 28 day infusion bleeding event rate was higher but symmetrically higher for both groups.

DR. SIEGEL: I probably should ask for clarification. Please correct me if I am wrong, Dr. Lindblad. As defined in these slides, infusion period includes not only while the infusion is running, but I think what the next day to day and a half, depending on the time of day it was stopped. So, it includes essentially the period in which at least we anticipate there is sufficient drug on board to have an impact on coagulation. Whether there are long term, subtle effects that we don't know about of the drug, of course, we could only speculate.

DR. RELLER: Dr. Archer.

DR. ARCHER: I wonder if the sponsor could comment on one of the FDA slides that showed there was no difference in mortality as a function of protein C levels.

DR. MACIAS: The protein C status at baseline was the only a priori defined subgroup that we felt we might detect differential effect in. In fact, we thought people that were protein C deficient would benefit more from the administration of activate protein C. I think there is a